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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,168	02/07/2001	David J. Wright	P-4423D1	8991

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EXAMINER	
FORMAN, BETTY J	

ART UNIT	PAPER NUMBER
1634	6

DATE MAILED: 03/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/778,168	Applicant(s) WRIGHT ET AL.	
	Examiner BJ Forman	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to papers filed 7 January 2002 in Paper No. 5 in which claims 1, 3-5, 13, 17, 19, 20 and 22 were amended and claim 2 was canceled. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 3 dated 5 July 2001 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 103(a) are maintained. All of the arguments have been thoroughly reviewed and are discussed below.

The examiner's Art Unit has changed from 1655 to 1634. Please address future correspondence to Art Unit 1634.

Currently claims 1 and 3-22 are under prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 3-5, 7-12, 14-18 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42).

Regarding Claim 1, Newton et al. disclose a method for detecting a single nucleotide polymorphism in a target comprising: hybridizing a detector primer to the target, wherein the

detector primer comprises a diagnostic nucleotide for the single nucleotide polymorphism and is complementary to the target sequence; amplifying the target by hybridization and extension of the detector primer (Column 4, lines 31-67); determining efficiency of the detector primer extension; and detecting the presence or absence of the single nucleotide polymorphism based on the efficiency of the detector primer extension (Column 13, lines 11-34) wherein the amplification reaction is an isothermal reaction i.e. performed at the melting temperature of the sequence (Column 7, lines 50-60) and wherein the diagnostic nucleotide is a terminal nucleotide complementary to the polymorphism (Column 4, lines 35-37) but they do not teach the diagnostic nucleotide is about one to four nucleotides from a 3' terminal nucleotide. However, diagnostic nucleotides adjacent to the 3' terminal nucleotide were well known in the art at the time the claimed invention was made as taught by Reynolds et al. and Krausa et al. Specifically, Reynolds et al. teach a similar method for detecting a single nucleotide polymorphism in a target sequence comprising: hybridizing a detector primer comprising a diagnostic nucleotide to the target; amplifying the target and detecting the presence or absence of the single nucleotide polymorphism, wherein the amplification reaction is an isothermal amplification reaction (Column 3, lines 17-45 and Column 11, lines 5-20 and Column 12, lines 59-67) and wherein the diagnostic nucleotide is near the 3' end of the terminal nucleotide (Column 11, lines 11-16). Additionally, Krausa et al. teach diagnostic primer comprising a diagnostic nucleotide about one to four nucleotides from the 3' end wherein the primers identify polymorphic sites and provide for fine mapping of polymorphisms (page 38, left column, lines 8-20). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Reynolds et al. wherein the diagnostic primer is near the 3' end of the terminal nucleotide of the diagnostic primer to the terminal nucleotide diagnostic primers of Newton et al. to provide diagnostic primers having a diagnostic nucleotide about one to four nucleotides from the 3' terminal nucleotide of the diagnostic primer based on the known location of a polymorphism as taught by Krausa et al. for the

obvious benefit of polymorphism-specific detection and complete polymorphism mapping as taught by Krausa et al. (page 38, left column, lines 8-20).

Regarding Claim 3, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using two or more detector primers comprising different diagnostic nucleotides (Column 30, Example 1).

Regarding Claim 4, Newton et al. teach the method wherein two detector primers are used to identify which of two possible alleles is present in the target sequence (Column 30, Example 1).

Regarding Claim 5, Newton et al. teach the method wherein four detector primers are used to identify the nucleotide present in the target sequence at the position of the single nucleotide polymorphism (Column 32, Example 4).

Regarding Claim 7, Newton et al. teach the method wherein the detector primer further comprises a nucleotide which forma a nondiagnostic mismatch with the target sequence (Column 12, lines 22-26).

Regarding Claim 8, Newton et al. teach the method wherein the nondiagnostic nucleotide is positioned within fifteen nucleotides of the diagnostic nucleotide in the detector primer (Column 12, lines 27-32).

Regarding Claim 9, Newton et al. teach the method wherein the nondiagnostic nucleotide is positioned 1-5 nucleotides from the diagnostic nucleotide in the detector primer (Column 12, lines 27-32).

Regarding Claim 10, Newton et al. teach the method wherein the nondiagnostic nucleotide adjacent to the diagnostic nucleotide in the detector primer i.e. 1, 2 or 3 bases from the terminal nucleotide (Column 12, lines 27-32).

Regarding Claim 11, Newton et al. teach the method wherein the detector primer is about 15-36 nucleotides long (Column 11, lines 12-20).

Regarding Claim 12, Newton et al. teach the method wherein the detector primer is about 18-24 nucleotides long (Column 11, lines 12-20).

Regarding Claim 14, Newton et al. teach the method wherein the detector primer is about 12-50 nucleotides long (Column 11, lines 12-20).

Regarding Claim 15, Newton et al. teach the method wherein the detector primer is about 12-24 nucleotides long (Column 11, lines 12-20).

Regarding Claim 16, Newton et al. teach the method wherein the detector primer is about 12-19 nucleotides long (Column 11, lines 12-20).

Regarding Claim 17, Newton et al. teach the method wherein the presence or absence of the single nucleotide polymorphism is detected by means of a label associated with the detector primer (Column 14, lines 40-48).

Regarding Claim 18, Newton et al. teach the method wherein the label becomes detectable upon extension of the detector primer (Column 8, lines 13-23).

Regarding Claim 21, Newton et al. teach the method wherein the efficiency of detector primer extension is determined quantitatively i.e. detection of heterozygous or homozygous samples (Column 13, lines 35-41).

Response to Arguments

4. Applicant argues that Newton only teaches use of a 3' terminal nucleotide as a diagnostic nucleotide wherein their 3' terminal nucleotide differentiates between targets containing the SNP from those that do not contain the SNP, wherein the differentiation is based on the complementarity of the 3' terminal nucleotide. Applicant further argues that one of ordinary skill in the art reading Reynolds would not be motivated to use primers that hybridize to the target sequence such that the polymorphic site hybridizes at or near the 3' end of the primer because Reynolds is consistent with Newton in teaching the necessity of carrying out the amplification reaction using a diagnostic primer having complementarity at the 3' end. Applicant argues that, because Reynolds teach the necessary characteristic for detecting/identifying a SNP in an amplification reaction is consistent with Newton and because Reynolds do not teach an embodiment wherein a target polymorphic site hybridizes at or near the 3' end, one of skill in the art would not have been motivated to combine the teaching of Newton and Reynolds to obtain the claimed invention. Finally, Applicant argues that the

teachings of Krausa do not provide any teaching that, combined with that of Newton would render the claimed invention obvious.

The arguments have been considered but are not found persuasive because as stated above, Reynolds specifically teach primers for detecting a single polymorphic site wherein the primer hybridizes to the target such that the polymorphic site is at or near the 3' end of the primer (Column 11, lines 11-14). While Reynolds do not teach an embodiment wherein the primer is complementary to a polymorphic site near the primers' 3' end, Krausa teach a similar method wherein the diagnostic primer comprises a diagnostic nucleotide about one to four nucleotides 5' of the 3' terminal nucleotide (Tables 2A and 2B) and wherein the primer is complementary to the polymorphism being detected (figure legend, bottom of page 37). The primers of Krausa provide the necessary characteristic for the amplification of Newton and Reynolds i.e. complementarity between target and primer at the primer's 3' end. Therefore, one skilled in the art would have been motivated by the primer teaching of Krausa to modify the primers of Newton as suggested by Reynolds to derive diagnostic primers having a diagnostic nucleotide one to four nucleotides 5' of the 3' end.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the diagnostic nucleotide near the 3' end of the primer as suggested by Reynolds et al. to the diagnostic primers of Newton et al. and to design diagnostic primers having a diagnostic nucleotide about one to four nucleotides from the 3' terminal nucleotide of the diagnostic primer based on the known location of a polymorphism as taught by Krausa et al. for the obvious benefit of polymorphism-specific detection and complete polymorphism mapping as taught by Krausa et al. (page 38, left column, lines 8-20).

5. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No.

5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42) as applied to Claim 1 above and further in view of Mullis et al. (U.S. Patent No. 4,683,195, issued 28 July 1987).

Regarding Claim 6, Newton et al. teach the method wherein the detector primer has a 5' tail sequence (Column 11, lines 40-45) but they do not teach each of the multiple primers has a different 5' sequence. Reynolds et al. teach the similar method wherein the detector primer has a 5' tail sequence wherein the 5' tail sequence facilitates cloning and sequencing as taught by Mullis et al. (Column 11, lines 21-27) and Mullis et al. teach multiple primers comprise a different 5' tail sequence to facilitate cloning and sequencing of individual amplified products (Column 15, lines 38-47). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' tail sequence of the detector primers taught by Newton et al. and Reynolds to provide each detector primer with a different 5' tail sequence for the expected benefit of facilitating cloning and sequencing of individual amplified products as taught by Mullis et al. (Column 15, lines 38-47) to thereby simplify identification of individual single nucleotide polymorphic loci.

Response to Arguments

6. Applicant argues that the remarks regarding Claim 1 are equally applicable to the rejection of Claim 6. The arguments regarding Claim 1 have been considered and are addressed above.

7. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42) as applied to Claim 1 above and further in view of Guatelli et al. (Proc. Natl. Acad. Sci. USA, 1990, 87: 1874-1878).

Regarding Claim 13, Newton et al. teach the method is an isothermal amplification reaction (Column 7, lines 50-60) but they do not teach the reaction is selected from SDA, 3SR, NASBA and TMA. Reynolds et al. teach the similar method comprising 3SR amplification (Column 12, lines 59-67). Additionally, Guatelli et al. teach 3SR amplification and motivation for applying 3SR amplification in target detection i.e. 3SR amplification produces ten-million fold amplification in less than two hours which is useful for detecting targets of low abundance (Abstract). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the 3SR amplification of Reynolds et al. to the similar isothermal amplification of Newton et al. for the expected benefits of detecting rare or low copy number target sequences as taught by Guatelli et al. (Abstract).

Response to Arguments

8. Applicant argues that the remarks regarding Claim 1 are equally applicable to the rejection of Claim 13. The arguments regarding Claim 1 have been considered and are addressed above.

9. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42) as applied to Claim 1 above and further in view of Chen et al. (Nucleic Acids Research, 1997, 25(2): 347-353).

Regarding Claims 19 and 20, Newton et al. teach the method wherein the presence or absence of the single nucleotide polymorphism is detected by means of a label associated with the detector primer, wherein the label becomes detectable upon extension of the detector primer (Column 8, lines 13-23) but they do not teach the label is a fluorescent donor/quencher dye pair (Claim 19) and they do not teach a change in fluorescence is detected as an indication

of the presence of the single nucleotide polymorphism (Claim 20). However, Chen et al. teach a similar method for detecting a single nucleotide polymorphism comprising hybridizing a detector primer to the target; amplifying the target by extension of the detector primer; and detecting the single nucleotide polymorphism and wherein the single nucleotide polymorphism is detected by a label associated with the detector primer, wherein the label produces a change in signal upon extension of the detector primer and wherein the label is a fluorescent donor/quencher pair and a decrease in donor dye (page 348, right column, first and second full paragraphs). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fluorescence donor/quencher dye pair of Chen et al. wherein a change in fluorescence determines the presence of the single nucleotide polymorphism to the fluorescence detection of single nucleotide polymorphism of Newton et al. for the expected benefits of highly sensitive and specific detection of primer extension product as taught by Chen et al. (page 348. right column, second full paragraph).

Response to Arguments

10. Applicant argues that the remarks regarding Claim 1 are equally applicable to the rejection of Claims 19 and 20. The arguments regarding Claim 1 have been considered and are addressed above.

11. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42) as applied to Claim 1 above and further in view of Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696).

Regarding Claim 22, Newton et al. do not teach the method wherein prior to amplifying, the detector primer is displaced from the target by extension of an upstream primer. However,

Strand Displacement Amplification was well known in the art at the time the claimed invention was made as taught by Walker et al. Specifically, Walker et al. teach hybridizing a detector primer to a target, displacing the detector primer from the target by extension of an upstream primer and amplifying the target (page 1692, Fig. 1) wherein displacement generates target sequence of defined 3' and 5' ends with increased efficiency and decreased non-specific primer binding (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the amplification of Newton et al. by extending an upstream primer to displace the detector primer prior to amplification of the target sequence for the expected benefits of increased efficiency and decreased non-specific product formation as taught by Walker et al. (Abstract) to thereby efficiently and accurately detect a single nucleotide polymorphism.

Response to Arguments

12. Applicant argues that the remarks regarding Claim 1 are equally applicable to the rejection of Claim 22. The arguments regarding Claim 1 have been considered and are addressed above.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
March 21, 2002

W. Gary Jones
Supervisory Patent Examiner
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